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Descriptive and risk factor analysis for choanal atresia: The National Birth Defects Prevention Study, 1997–2007

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Abstract

Choanal atresia causes serious posterior nasal obstruction. This defect is the leading cause of nasal surgery in newborns, although its etiology is largely unknown. Data from the National Birth Defects Prevention Study, a population-based case–control study, were used to examine associations between maternal self-reports of exposures and occurrence of choanal atresia in their offspring. Overall, 117 case and 8350 control mothers with deliveries from 1997 through 2007 provided telephone interview reports of pre-pregnancy (one year before conception) and periconceptional (one month before through three months after conception) exposures. The exposures analyzed were pre-pregnancy dietary intake, pre-pregnancy and periconceptional caffeine consumption, and periconceptional cigarette smoking, alcohol drinking, and medication use. Independent associations between each exposure and all choanal atresia cases combined (n = 117) and isolated choanal atresia cases (those without additional unrelated major defects; n = 61) were examined. Odds ratios (ORs), both unadjusted (uORs) and adjusted (aORs) for potential confounders, and 95% confidence intervals (CIs) were estimated using unconditional logistic regression analysis. For all choanal atresia cases combined, positive associations were observed with maternal pre-pregnancy intake in the highest quartile for vitamin B-12 (aOR = 1.9; CI = 1.1,3.1), zinc (aOR = 1.7; CI = 1.0,3.1), and niacin (aOR = 1.8; CI = 1.0,3.1), and intake in the lowest quartile for methionine (aOR = 1.6; CI = 1.0,2.6) and vitamin D (aOR = 1.6; CI = 1.0,2.4) compared to intake in the two intermediate quartiles combined. Further, a positive association was observed with periconceptional use of thyroid medications (uOR = 2.6; CI = 1.0,6.3) compared to no use of such medications. Among isolated choanal atresia cases, negative associations were observed for pantothenic acid (aOR = 0.4; CI = 0.2,0.9) and fat (aOR = 0.5; 95% CI = 0.2,1.0)

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intake in the lowest quartile compared to that in the intermediate quartiles, and positive associations were observed for periconceptional cigarette smoking (aOR = 2.3; CI = 1.1,4.7) compared to no smoking and pre-pregnancy daily coffee intake of 3 or more cups (aOR = 2.5; CI = 1.1,5.6) compared to intake of less than 1 cup per day. The positive association for periconceptional exposure to thyroid medications also persisted for isolated choanal atresia cases (uOR = 4.0; CI = 1.1,11.2). Because of the large number of associations tested, these findings may be due to chance. Alternatively, they may contribute new hypotheses regarding the etiology of choanal atresia; thus, requiring replication in additional studies.

Keywords

Alcohol drinking; Caffeine; Choanal atresia; Cigarette smoking; Diet

1. Introduction

Choanal atresia is a well-recognized craniofacial defect characterized by occlusion in the posterior nasal passage [Hengerer et al., 2008]. Published prevalence estimates for choanal atresia range from 1 to 2 per 10,000 live births [Case and Mitchell, 2011; Harris et al., 1997], and this defect has been reported to be twice as common in females as males [Samadi et al., 2003]. Approximately one-half of all choanal atresia diagnoses are bilateral; unilateral presentation predominantly affects the right nasal passage [Ramsden et al., 2009]. Bilateral choanal atresia is the most common indication for surgical intervention involving the nose in infants [Friedman et al., 2000].

Choanal atresia is thought to be a multifactorial trait, although neither genetic variants nor environmental (i.e., non-genetic) exposures for this malformation have been well-studied. Some previously published studies have suggested that choanal atresia tends to occur sporadically and to recur infrequently in siblings and in successive generations [Bhattacharyya and Lund, 1996; Gershoni-Baruch, 1992; Skolnik et al., 1973]. Other studies have suggested single gene models that include both autosomal dominant and autosomal recessive transmission [Gershoni-Baruch, 1992].

To date, two population-based descriptive studies of choanal atresia (or severe stenosis) were identified. One study investigated 444 choanal atresia/severe stenosis cases from birth defect registries in California, Sweden, and France for the years 1976 through 1992 [Harris et al., 1997]. The other study analyzed data for 202 choanal atresia/severe stenosis cases from the Texas Birth Defects Registry (TXBDR) [Case and Mitchell, 2011]. Each study observed a small excess in choanal atresia/severe stenosis among non-Hispanic white mothers compared to mothers of other race/ethnicities, neither study observed an excess in female compared to male offspring, nor associations with maternal age, and about one-half of cases presented with associated defects, excluding chromosomal defects.

The CHARGE (Coloboma, Heart Defect, Atresia of Choanae, Retarded Growth and Development, Genital Anomaly, Ear Defect) syndrome is a common phenotype associated with choanal atresia [Aramaki et al., 2006; Harris et al., 1997; Jongmans et al., 2006; Leclerc and Fearon, 1987]. With the discovery of the association between mutations in the

chromodomain helicase DNA binding protein 7 (*CHD7*) gene and CHARGE syndrome [Johnson et al., 2006; Vissers et al., 2004], a recent review and pooling of data from 26 studies with 247 total *CHD7*-mutation positive CHARGE cases estimated that 95 (38%) cases presented with choanal atresia [Zentner et al., 2010]. Another recent study found that 99 of 280 (35%) *CHD7*-mutation positive CHARGE cases presented with choanal atresia; however, clinical data were possibly incomplete for 101 cases [Bergman et al., 2011]. Excluding these 101 cases increased the proportion of *CHD7*-mutation positive CHARGE with choanal atresia to 55%.

With regard to nonsyndromic choanal atresia (i.e., those cases without a well-recognized single-gene or chromosomal abnormality), a commonly proposed molecular theory is disruption of neural crest cell migration between the 4th and 11th weeks of gestation [Corrales and Koltai, 2009; Dunham and Miller, 1992; Hengerer et al., 2008]. Exposures, such as alcohol, retinoic acid, and anti-thyroid medication use, that are thought to influence neural crest cell migration may contribute to choanal atresia. In mice, suppression of retinoic acid synthesis due to mutations in the aldh1a3 gene induced choanal atresia and other malformations of the nasal cavity [Dupe et al., 2003], and persistent local activation of fibroblast growth factor pathways among knockout mice (aldh1a3 null mutants) induced choanal atresia [Hehr and Muenke, 1999]. In humans, a case report [Krapels et al., 2006] and three case-series [Bowman and Vaidya, 2011; Koenig et al., 2010; Ting et al., 2013] described the co-occurrence of choanal atresia, hearing loss, and developmental delay, as well as developmental abnormalities of the gastrointestinal tract, nipples, and the face (together termed `carbimazole embryopathy') in offspring of mothers who used this anti-thyroid medication during pregnancy. Several additional case studies [Barbero et al., 2004; Greenberg, 1987; Johnsson et al., 1997], as well as a case–control study [Barbero et al., 2008], have described the occurrence of choanal atresia in offspring of mothers who reported prenatal use of anti-thyroid medication methimazole or propranolol. More recently, a case–control study using data from the TXBDR reported a positive association for isolated choanal atresia/severe stenosis among offspring born to mothers with residential exposure to the herbicide atrazine [Agopian et al., 2013]. Little attention has been given to additional environmental exposures that may contribute to choanal atresia.

The hypothesized role of neural crest cell migration in the development of choanal atresia and the potential for this migration to be disrupted by environmental exposures during pregnancy suggest the need for a comprehensive, population-based etiological investigation of this defect. As such, an analysis of data from a multisite, population-based case–control study, the National Birth Defects Prevention Study (NBDPS), was conducted. This analysis of NBDPS data permitted examination of the independent associations between several selected exposures and choanal atresia, while adjusting for relevant covariables.

2. Materials and methods

The NBDPS, established by the Centers for Disease Control and Prevention (CDC) in 1996, is an ongoing, multisite, population-based case–control study of environmental exposures and gene variants for over 30 major structural birth defects [Yoon et al., 2001]. Choanal atresia cases and unaffected controls with an estimated date of delivery (EDD) on or after

October 1, 1997 were ascertained from the population-based surveillance system at each site. A systematic data-collection protocol was used to consent and administer a telephone interview to case and control mothers. The interviews were conducted no earlier than 6 weeks and no later than 24 months after the EDD. NBDPS sites that contributed data to the current analyses were Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), New Jersey (NJ), New York (NY), North Carolina (NC), Texas (TX), Utah (UT), and the CDC in Metropolitan Atlanta, Georgia.

2.1. Subject selection

For the NBDPS, choanal atresia was defined as a congenital obstruction of the posterior choana(e) and coded using the modified British Paediatric Association (BPA) codes implemented by the CDC (748.010: choanal atresia, laterality unknown; 748.011: choanal atresia; unilateral, left; 748.012: choanal atresia, unilateral, right; 748.013: choanal atresia, unilateral, side-unknown; 748.014: choanal atresia, bilateral). Choanal atresia cases identified included live births (all NBDPS sites), fetal deaths (AR, CA, CDC, IA, MA, NY [since year 2000], TX [since year 2000], UT), and elective terminations (AR, CA, CDC, IA, NY [since year 2000], TX [since year 2000], UT). Those with an EDD from October 1, 1997 (CA, CDC, IA, MA, NY, TX), January 1, 1998 (AR, NJ), or January 1, 2003 (NC, UT) through December 31, 2002 (NJ) or December 31, 2007 (AR, CA, CDC, IA, MA, NC, NY, TX, UT) were ascertained. Clinical geneticists at each NBDPS site confirmed the diagnosis of choanal atresia by review of data abstracted from medical records. All identified choanal atresia cases were reviewed by a second clinical geneticist (J.C.C.) and included as choanal atresia if documented on CT scan or by examination at time of treatment (surgery or laser) or at postmortem; cases were then classified as `isolated' if the case did not have an additional, unrelated major birth defect. Alternately, if one or more such defects were present (not including the CHARGE syndrome) the case was classified as `multiple, with no CHARGE.' For one case, choanal atresia was determined to present as part of the CHARGE syndrome based on phenotypic characteristics reported; however, data on *CHD7* mutations were not available for any choanal atresia case. Choanal atresia cases that were part of a known genetic syndrome or complex were excluded from the NBDPS [Rasmussen et al., 2003]. Choanal stenosis, including pyriform aperture stenosis, was also excluded. NBDPS control infants were a random sample of unaffected live births delivered in the same time frame and in the same region (e.g., surveillance catchment area) as choanal atresia cases. Control infants were selected from birth certificates (AR [2000–2007], CDC [2001–2007], IA, MA, NC, NJ, UT) or hospital delivery records (AR [1997–2000], CA, CDC [1997–2000], NY, TX); selection of controls from hospital records was proportional to the total number of births in each hospital in the respective surveillance region. For both choanal atresia cases and controls, those who were adopted or in foster care or whose biological mothers were deceased or did not speak English or Spanish were excluded.

2.2. Exposure assessment

2.2.1. Diet—Maternal dietary exposures during the one year before pregnancy (pre-pregnancy) were assessed using 58 food items from the Willett Food Frequency Questionnaire [Willett et al., 1987]. The U.S. Department of Agriculture version S19 nutrient database was used to calculate estimates of individual nutrient values from the

reported food items [U.S. Department of Agriculture and Agricultural Research Service, 2006]. Folic acid intake was also calculated from prenatal multivitamins, mineral supplements, non-prenatal multivitamins, and other supplements containing folic acid.

2.2.2. Caffeine—Maternal pre-pregnancy caffeine exposure was estimated using the responses in the food frequency questionnaire to chocolate consumption and in the NBDPS beverage module for consumption of caffeinated beverages (coffee, tea, and soda) as calculated in previous NBDPS analyses [Browne et al., 2007]. Specifically, exposure for coffee and tea were measured as average number of cups per day, and exposure for soda was measured as average number of cans, glasses, or bottles per day. Using the total caffeine consumption, categories were created for none or very low (<100 mg/day), low (100–<200 mg/day), moderate (200–<300 mg/day), and high or very high intake (≥300 mg/day). Each mother was also asked if her intake of caffeinated coffee, tea, and soda was more, the same, or less during the index pregnancy compared to her pre-pregnancy report. Caffeine exposure from medications was not examined due to the infrequently reported intake among case mothers.

2.2.3. Cigarette smoking—Maternal exposure to cigarette smoking was assessed for the three months prior to conception (labeled B3, B2, and B1) and the duration of the pregnancy (labeled M1, M2, M3 for the first three months of pregnancy; T2 for second trimester; and T3 for third trimester). Cigarette smoking was classified as `active' if a mother reported that she smoked cigarettes and `passive' if she reported an indirect exposure. A positive response to active cigarette smoke exposure was followed by further inquiry about the specific month(s) or trimester(s) smoked and the average number of cigarettes smoked per day during each time period. A positive response to passive exposure to cigarette smoke was followed by inquiry into whether the exposure occurred in the household, workplace, or both, and the specific month(s) or trimester(s) during which the exposure(s) occurred. For the current analysis, cigarette smoking exposures were restricted to the periconceptional period, which corresponded to the month prior to conception (B1) through the first three months of pregnancy (M1, M2, and M3).

2.2.4. Alcohol—Consumption of alcoholic beverages (beer, wine, mixed drinks, or shots of liquor) was collected monthly or by trimester as described above for cigarette smoking. For each time period that a mother reported consumption, the average number of drinking days, average number of drinks per drinking day, and the maximum number of drinks on one occasion were requested. Like cigarette smoking exposures, analysis of alcohol consumption was limited to exposure during the periconceptional period.

2.2.5. Medications—Pre-pregnancy and pregnancy related maternal illnesses (e.g., diabetes, hypertension, seizures, respiratory illness, pelvic inflammatory disease, infections of the kidney, bladder, and urinary tract, and other fevers or illnesses) were queried. For each reported illness, type of medication used, estimated dates of use, and frequency and duration of use were also queried. Exposure dates were re-coded into monthly exposure periods for each of the three months before the pregnancy, and each month of the pregnancy. Analysis of medications was limited to the periconceptional period. Reported medications

were linked to their active ingredients using the Slone Epidemiology Center Drug Dictionary [Kelley et al., 2003]. The medication classes were predefined by the NBDPS.

2.3. Statistical analysis

Selected case and control characteristics (sex, birth weight, gestational age at delivery, plurality, and family history of choanal atresia), maternal characteristics (age at delivery, race/ethnicity, education, pre-pregnancy body mass index [BMI], parity, nativity, folic acid use, type 1 or 2 diabetes before index pregnancy, history of hypertension, season of conception, and periconceptional exposure to cigarette smoking and alcohol) and study site were compared between case and control mothers using the Pearson chi-square test or Fisher's exact test (expected cell frequencies <5). Unadjusted odds ratios (uORs) and 95% confidence intervals (CIs) were estimated to investigate the associations between choanal atresia and maternal dietary intake, caffeine consumption, cigarette smoking, alcohol consumption, and selected medication use as categorical variables. For dietary analyses, case and control mothers whose dietary intakes were missing or produced an extreme average total energy intake in kilocalories per day (e.g., <500 or >5000 kilocalories per day) were excluded. Following exclusions, quartiles were derived from the intake distribution among the control mothers. Associations between choanal atresia and intake of individual macronutrients, one-carbon compounds, and single vitamins were examined by comparing either the lowest quartile (<25th percentile) or highest quartile of intake (>75th percentile) to the intermediate quartiles of intake (25th – 75th percentiles). The intermediate quartiles were chosen as a reference level to examine associations with both high and low maternal dietary intake.

Multivariable analyses involved fitting unconditional logistic regression models. Each selected infant and maternal characteristic was evaluated as a potential confounder by examining the difference in the magnitude of the exposure effect estimates with and without the covariables in the model. Initially all covariables were included in the model; they were manually removed one at a time. A covariable was retained for inclusion in the multivariable models if the exposure estimate changed by 15% when the covariable was deleted from the model. Different covariables were selected for different exposures based on confounder evaluation described above. In addition to the characteristics listed above, confounding due to caffeine exposure was examined for periconceptional cigarette smoking (yes/no) and alcohol consumption (yes/no) models. For ordinal exposures, such as average number of cigarettes/day or average drinks/month, a dose–response effect was tested using the Cochran–Armitage trend test.

Adjusted analyses were conducted separately for all choanal atresia cases combined and for isolated choanal atresia cases; analyses of multiple choanal atresia cases with or without the CHARGE syndrome were not examined because of the modest sample sizes. Selected medication classes, identified from previous findings for choanal atresia (thyroid and anti-thyroid medications) or orofacial clefts (anti-epileptics, acne medications [isotretinoin], retinoids, corticosteroids, and non-steroidal anti-inflammatory agents) and not previously examined for choanal atresia using NBDPS data, were chosen for analysis. Analyses of medication class exposures were restricted to unadjusted analyses only because of the small

number of exposed case mothers. All statistical analyses were conducted using SAS, version 9.2 (SAS, Cary, NC).

3. Results

Of the eligible NBDPS choanal atresia cases identified with EDDs from October 1, 1997 through December 31, 2007, 117 (67%) case mothers and mothers of 8350 (65%) control infants completed the telephone interview. The median time between EDD and interview was 9.0 months and 7.8 months for case and control mothers, respectively.

Comparison of selected characteristics between all choanal atresia cases combined and controls showed that cases were more likely to be female, have low birth weight (<2500 g), be preterm (<37 weeks of gestation), and have a family history of choanal atresia (Table 1). Also, approximately one-half of cases presented with isolated choanal atresia and approximately one-half of cases presented with bilateral atresia; unilateral cases were predominantly right-sided. Because of limited data, histological characteristics (bony vs. membranous) of each defect could not be examined. Mothers of choanal atresia cases were more likely to be older (≥35 years of age), non-Hispanic white, have type 1 or 2 diabetes before pregnancy, and a fall or winter season of conception compared to those of controls. Comparison of isolated cases and controls, as well as their mothers, tended to reveal similar findings; additionally, mothers of isolated cases were significantly more likely to be natives of the United States and to report active periconceptional cigarette smoking than those of controls. The proportion of isolated cases recruited differed across the ten study sites.

3.1. Diet

Dietary analyses were based on 113 case mothers (59 isolated cases) and 8228 control mothers after the previously mentioned exclusions. For all choanal atresia cases combined, positive associations were observed for maternal pre-pregnancy intake in the highest quartile compared to intake in the intermediate quartiles for vitamin B-12 (aOR = 1.9; 95% CI = 1.1,3.1), zinc (aOR = 1.7; 95% CI = 1.0,3.1), and niacin (aOR = 1.8; 95% CI = 1.0,3.1) (Table 2). Positive associations were also observed for intake in the lowest quartile compared to that in the two intermediate quartiles combined for methionine (aOR = 1.6, 95% CI = 1.0,2.6) and vitamin D (aOR = 1.6; 95% CI = 1.0,2.4). For isolated cases, a negative association was observed for both pantothenic acid intake (aOR = 0.4; 95% CI = 0.2,0.9) and fat intake (aOR = 0.5; 95% CI = 0.2,1.0) in the lowest quartile compared to that in the intermediate quartiles.

3.2. Caffeine consumption

Maternal pre-pregnancy reports of different amounts of caffeinated coffee, tea, and soda consumption compared to no reported pre-pregnancy consumption produced aORs near or below unity for all choanal atresia cases combined. Conversely, for isolated cases, a dose–response effect (Cochran–Armitage trend test p-value<0.05) was found for reports of pre-pregnancy coffee consumption of 1–2 cups per day (aOR = 1.7; 95% CI = 1.0,3.1) and of 3 or more cups per day (aOR = 2.5; 95% CI = 1.1,5.6) compared to less than 1 cup per day. The aORs for reported caffeinated tea or soda consumption were near or below unity for

isolated cases. Cumulative exposure to caffeine from all sources queried (coffee, tea, soda, and chocolate) tended to show weakly positive or negative aORs for all cases combined and positive, but nonsignificant, aORs for isolated cases. Analyses were rerun following exclusion of mothers who reported a change in intake. This exclusion did not materially change the aORs observed (data not shown); thus, aORs for all mothers are presented in Table 3.

3.3. Cigarette smoking

Compared to control mother reports of any periconceptional exposure to cigarette smoking, reports from mothers of all choanal atresia cases combined tended to be similar and reports from mothers of isolated cases tended to be higher (Table 4). Among all mothers who reported active cigarette smoking, most were exposed during all four periconceptional months (data not shown). Associations for all cases combined were near unity for active exposure only, weakly positive for passive exposure only, and negative for combined active and passive exposure. By comparison, those for isolated cases were two-fold higher for active exposure only (aOR = 2.3; 95% CI = 1.1,4.7), weakly positive for passive exposure only, and negative for combined active and passive exposure.

3.4. Alcohol consumption

Reports of any periconceptional alcohol consumption were similar between case mothers (either all cases combined or isolated cases) and mothers of controls (Table 4). Consumption was higher in the month before conception (B1) among most case and control mothers and gradually decreased in the remainder of the periconceptional months (data not shown). Associations for any alcohol consumption in either case group were near unity, as were those for average drinks consumed per month, and reports of binge episodes (four or more drinks per occasion).

3.5. Medications

Maternal periconceptional exposure was largely null for each medication class examined, except for thyroid medications. For all choanal atresia cases combined, unadjusted analyses showed a positive association with maternal exposure to thyroid medications (exposed cases = 5 and exposed controls = 145; uOR = 2.6; 95% CI = 1.0,6.3) compared to no exposure. A positive association also persisted for maternal exposure to thyroid medications among isolated cases (exposed cases = 4; uOR = 4.0; 95% CI = 1.1,11.2). Three out of five mothers who reported use of thyroid medications were exposed to synthroid (uOR = 4.0; 95% CI = 1.1,11.2).

4. Discussion

This is the first population-based case–control study of which we are aware to examine associations between maternal dietary intake, caffeine, cigarette smoking, alcohol, medications, and choanal atresia. For all choanal atresia cases combined, positive associations were observed for high maternal pre-pregnancy intake of vitamin B-12, zinc, and niacin, but low intake of methionine and vitamin D. Positive, unadjusted associations were observed for periconceptional use of thyroid medications. Restriction of analyses to

isolated cases, a more phenotypically homogeneous group, produced positive associations for lower levels of maternal pre-pregnancy intake of pantothenic acid and low fat diet, increased intake of caffeinated coffee, and periconceptional active cigarette smoking; the positive unadjusted association with periconceptional use of thyroid medication also persisted.

Although the current findings may contribute new hypotheses to the etiology of choanal atresia, placing these findings in the context of those from previous investigations is limited by the lack of previously published reports in humans that comprehensively examined environmental exposures for choanal atresia. In lieu of a direct comparison to previous research on choanal atresia, it may be appropriate to compare our observations to those previously reported for orofacial clefts, whose development is thought to be influenced, in part, by exposures that disturb neural crest cell migration. For example, animal studies have shown that neural crest cell migration can be disrupted by exposure to cigarette smoking [Sanbe et al., 2009], caffeine (reviewed in Nehlig and Debry [1994]), and alcohol [Cartwright and Smith, 1995; Chen and Sulik, 1996; Rovasio and Battiato, 2002], all common exposures during pregnancy [Tong et al., 2009; D'Angelo et al., 2007; Frary et al., 2005; Knight et al., 2004]. Also, animal models have shown that neural crest cell migration can be disrupted by exposure to anti-epileptic medication [Fuller et al., 2002], suboptimal levels of dietary nutrients, such as zinc [Rogers et al., 1995] and trace minerals [Keen et al., 2003], and elevated exposure to retinoids from either medication or dietary exposure (reviewed in Finnell et al. [2004]).

Previous studies of orofacial clefts in animals and humans did not find positive associations with high intake of vitamin B-12, zinc, or niacin (reviewed in Krapels et al. [2004]). In contrast, associations between deficiency of these nutrients and orofacial clefts have been consistently identified in rat models [Hurley and Swenerton, 1966; Keen et al., 2003; Rogers et al., 1995; Warkany and Petering, 1972], but less consistently in humans [Bille et al., 2007; Krapels et al., 2004, 2006; Munger et al., 2009; Shaw et al., 2006; Tamura et al., 2005]. The current findings for these nutrients, although positive, were of marginal significance and may have been due to chance. The positive association identified with low maternal intake of methionine, a one-carbon metabolism compound has also been identified as a risk factor for clefting in humans [Shaw et al., 2006], but not in animal models. Methionine acts as a methyl donor in the one-carbon metabolism pathway. Using methionine, selected enzymes maintain the homocysteine balance in the body, and any disturbance in the enzymes of the one-carbon pathway are associated with improper DNA synthesis and methylation, affecting both growth and tissue generation in the fetus [Baylin et al., 2000]. A positive association between low intake of vitamin D or pantothenic acid and orofacial clefts has not previously been reported in either animal or human studies. The association observed with vitamin D may be spurious, because only a small proportion of vitamin D intake is thought to come from dietary sources; in our analysis, we were unable to account for additional sources of vitamin D (e.g., sunlight).

The positive association observed between caffeinated coffee consumption and isolated choanal atresia is a novel finding, and supported by some human studies [Collier et al., 2009; McDonald et al., 1992; Mitchell et al., 2001], but not animal studies (reviewed in

Nehlig and Debry [1994]) for orofacial clefts. Residual confounding due to other unmeasured factors, however, cannot be ruled out. For example, high intake of coffee has also been associated with decreased iron absorption [Morck et al., 1983], although no significant association between dietary intake of iron and choanal atresia was observed in the current study. Also, caffeine from medications and weight loss supplements was not assessed due to paucity of exposed case mothers and difficulty in determining the amount of caffeine consumption from these exposures.

The positive association with maternal periconceptional active smoking and the lack of positive associations with maternal periconceptional alcohol consumption tend to parallel previous findings for clefting. Social stigma about alcohol use during pregnancy may have prevented some mothers from providing accurate reports of their exposure [Alvik et al., 2005].

Anti-thyroid medication use during pregnancy has been perhaps the most often identified risk factor for choanal atresia. Previous hospital-based studies have reported positive associations between methimazole and choanal atresia [Corrales and Koltai, 2009; Johnsson et al., 1997]. This association could not be adequately tested in the current study, as no case mothers reported exposure to thionomides or the anti-thyroid class of medications (e.g., methimazole or carbimazole), and only one case mother reported exposure to propylthiouracil. Alternatively, in the current study, an unadjusted association was observed with maternal periconceptional exposure to thyroid medications, most commonly Synthroid® use. Synthroid® is a prescription medication under the generic name, levothyroxine, and is commonly used to treat hypothyroidism. No previous animal or human studies have identified positive associations between Synthroid® or levothyroxine and choanal atresia. Because the literature on the placental transfer of levothyroxine has consistently shown it to be negligible [Briggs et al., 2005], the positive association observed between levothyroxine and choanal atresia in the current study may simply be a spurious finding. Use of other medications (anti-epileptics, acne medications [isotretinoin], retinoids, corticosteroids, and non-steroidal anti-inflammatory agents) suggested to be associated with orofacial clefts [Abrishamchian et al., 1994; Carmichael et al., 2007; Ericson and Kallen, 2001; Finnell et al., 2004], were not used by case mothers in the current study. Other associations examined between choanal atresia and selected medication classes from NBDPS were reported elsewhere (e.g., anti-bacterial [sulfonamides] [Crider et al. 2009]).

Limitations in the current study warrant caution in interpretation of the findings. Not all participating sites conducted active surveillance of stillbirths and elective terminations due to restrictive state laws; however, this should not have had considerable impact on study results as choanal atresia has not been associated with either pregnancy outcome. Also, genetic testing for the CHARGE syndrome was not available for any choanal atresia case; however, classification of choanal atresia with other major defects continuously evolved over the study time period in response to the discovery of the *CHD7* gene [Vissers et al., 2004] and the changing CHARGE syndrome diagnostic guidelines and regional practices. With regard to data collection, use of retrospective reports may have led to differential recall among case and control mothers; information bias was minimized using trained interviewers and systematic quality control measures. Also, several associations were based on modest

numbers of exposed case mothers, particularly those for medication use, producing rather imprecise confidence intervals. Related to this, some positive odds ratio estimates were of borderline statistical significance. Further, multiple associations were tested; thus, some associations identified may have occurred by chance, particularly because some associations were not supported by dose–response patterns.

The use of NBDPS data provides several strengths. The NBDPS is one of the largest case–control studies of birth defects in the U.S., covering almost 10% of annual births [Yoon et al., 2001]. This permits risk factor investigation for defects of low prevalence, such as choanal atresia. To identify cases, active surveillance approaches with multiple-source ascertainment were used to minimize referral-bias, a common problem reported in previous hospital-based studies of choanal atresia. Also, the diagnosis of choanal atresia and co-occurring birth defects was confirmed by systematic review by clinical geneticists [Rasmussen et al., 2003]. Additionally, NBDPS control infants were representative of the live births in each catchment area [Cogswell et al., 2009]. With regard to data collection, a computer-assisted telephone interview that included standardized prompts and systematic collection of exposures at different time frames during pregnancy aided mothers to identify and recall such exposures. This comprehensive collection of multiple exposures permitted statistical adjustment for potential confounders.

In summary, findings from the current study suggest that choanal atresia may be associated with sub-optimal pre-pregnancy exposure to selected nutrients and increasing daily exposure to coffee and periconceptional active cigarette smoking and selected medication use. Because of the large number of associations tested, these findings may be due to chance; however, they contribute new hypotheses regarding the etiology of choanal atresia which deserve investigation in additional population-based studies.

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Table 1

Selected characteristics of choanal atresia cases and controls and their birth mothers, The National Birth Defects Prevention Study, 1997–2007.

Characteristics	Controls (*N* = 8350)		All cases (*N* = 117)			Isolated cases (*N* = 61)		
	n	**(%)**	***n***	**(%)**		***n***	**(%)**	
Infant								
Sex								
Male	4241	(50.8)	41	(35.0)	*	18	(29.5)	*
Female	4101	(49.2)	76	(65.0)		43	(70.5)	
Birth weight (grams)								
≥2500	7849	(94.0)	80	(68.4)	*	54	(88.5)	*
<2500	466	(5.6)	37	(31.6)		7	(11.5)	
Gestational age at delivery (weeics)								
≥37	7562	(90.6)	80	(68.4)	*	49	(80.3)	*
<37	787	(9.4)	36	(31.0)		11	(18.0)	
Plurality								
1	8087	(96.9)	109	(93.2)		58	(95.1)	
2 or more	251	(3.0)	8	(6.8)		3	(4.9)	
Family history-choanal atresia								
No/don't know	8350	(100.0)	115	(98.3)	*	60	(98.4)	*
Yes	0	(0)	2	(1.7)		1	(1.6)	
Laterality								
Unilateral, left	–	–	14	(12.0)		7	(11.5)	
Unilateral, right	–	–	33	(28.2)		20	(32.7)	
Unilateral, side unknown	–	–	1	(0.9)		1	(1.6)	
Bilateral	–	–	63	(53.9)		31	(50.8)	
Laterality unknown	–	–	6	(5.0)		2	(3.4)	
Maternal								
Age at delivery (years)								
<25	2772	(33.2)	26	(22.2)	*	12	(19.7)	*
25–34	4404	(52.7)	66	(56.4)		33	(54.1)	
≥35	1174	(14.1)	25	(21.4)		16	(26.2)	
Race/ethnicity								
Non-Hispanic white	4940	(59.2)	85	(72.7)	*	50	(82.0)	*
Non-Hispanic black	927	(11.1)	8	(6.8)		4	(6.6)	
Hispanic	1908	(22.9)	20	(17.1)		6	(9.8)	
Other	545	(6.5)	3	(2.6)		0	(0)	
Education (years)								
<12	1429	(17.1)	18	(15.4)		6	(9.8)	
12	2016	(24.1)	23	(19.7)		15	(24.6)	
>12	4896	(58.6)	76	(65.0)		40	(65.6)	
Body Mass Index (kg/m^2)								

Characteristics	Controls (*N* = 8350)		All cases (*N* = 117)			Isolated cases (*N* = 61)		
	n	**(%)**	***n***	**(%)**		***n***	**(%)**	
<25	4837	(57.9)	67	(57.3)		34	(55.7)	
≥25	3172	(38.0)	44	(37.6)		25	(41.0)	
Parity								
0	2435	(29.2)	36	(30.8)		14	(23.0)	
1	2454	(29.4)	34	(29.1)		19	(31.2)	
≥2	3459	(41.4)	47	(40.2)		28	(45.9)	
Nativity								
United States	6672	(80.0)	95	(81.2)		56	(91.8)	*
Other	1673	(20.0)	22	(18.8)		5	(8.2)	
Folk Acid [a]								
No	1049	(12.6)	12	(10.3)		5	(8.2)	
Yes	7193	(86.1)	105	(89.7)		56	(91.8)	
Type 1 or 2 diabetes before index pregnancy								
No	8286	(99.2)	114	(97.4)	*	59	(96.7)	*
Yes	51	(0.6)	3	(2.6)		2	(3.3)	
History of hypertension								
No	7218	(86.4)	105	(89.7)		56	(91.8)	
Yes	1122	(13.4)	12	(10.3)		5	(8.2)	
Season of conception								
Summer	2069	(24.8)	19	(16.2)	*	10	(16.4)	
Fall	2163	(25.9)	40	(34.2)		19	(31.6)	
Winter	2079	(24.9)	35	(29.9)		20	(32.8)	
Spring	2039	(24.4)	23	(19.7)		12	(19.7)	
Periconceptional cigarette smoking								
No	5664	(67.8)	77	(65.8)		36	(59.0)	*
Yes	2668	(32.0)	38	(32.5)		24	(39.3)	
Periconceptional alcohol consumption								
No	5239	(62.7)	71	(60.7)		36	(59.0)	
Yes	3039	(36.4)	44	(37.6)		24	(39.3)	
Study site								
Arkansas	1055	(12.6)	8	(6.8)		5	(8.2)	*
California	1017	(12.2)	10	(8.6)		1	(1.6)	
Iowa	927	(11.1)	10	(8.6)		5	(8.2)	
Massachusetts	1027	(12.3)	18	(15.4)		14	(23.0)	
New Jersey	573	(6.9)	14	(12.0)		6	(9.8)	
New York	722	(8.7)	13	(11.1)		11	(8.0)	
North Carolina	570	(6.8)	8	(6.8)		2	(3.3)	
CDC/Atlanta	880	(10.5)	15	(12.8)		7	(11.5)	
Texas	969	(11.6)	14	(12.0)		5	(8.2)	
Utah	610	(7.3)	7	(6.0)		5	(8.2)	

CDC, Centers for Disease Control and Prevention; *n*, frequency; kg, kilograms; m, meter; U.S., United States.

Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data.

* $p < 0.05$ for cases vs. controls.

[a] Any intake from prenatal, multivitamin, or folic acid as a single vitamin.

Table 2

Multivariable analyses for maternal dietary intake and choanal atresia, The Nationa Birth Defects Prevention Study, 1997–2007.

Exposure	Controls (*N* = 8228)	All cases (*N* = 113)		Isolated cases (*N* = 59)	
	N	*N*	aOR (95% CI)[a]	*N*	aOR (95% CI)[b]
Macronutrients					
Carbohydrate (g)					
Low	2057 (25.0)	37 (32.7)	1.0 (0.6,1.7)	18 (30.5)	0.7 (0.4,1.5)
Medium	4114 (50.0)	56 (49.6)	Referent	35 (59.3)	Referent
High	2057 (25.0)	20 (17.7)	1.1 (0.5,2.4)	6 (10.2)	0.5 (0.2,1.8)
Protein (g)					
Low	2057 (25.0)	39 (34.5)	1.3 (0.8,2.1)	17 (28.8)	0.6 (0.3,1.2)
Medium	4114 (50.0)	52 (46.0)	Referent	31 (52.5)	Referent
High	2057 (25.0)	22 (19.5)	1.3 (0.7,2.5)	11 (18.6)	1.6 (0.6,3.8)
Fat (g)					
Low	2057 (25.0)	36 (31.9)	1.1 (0.7,1.8)	15 (25.4)	0.5 (0.2,1.0)
Medium	4114 (50.0)	56 (49.6)	Referent	34 (57.6)	Referent
High	2057 (25.0)	21 (18.6)	1.1 (0.6,2.1)	10 (17.0)	1.4 (0.6,3.4)
Fiber (g)					
Low	2057 (25.0)	37 (32.7)	1.1 (0.7,1.8)	16 (27.1)	0.7 (0.4,1.3)
Medium	4114 (50.0)	54 (47.8)	Referent	34 (57.6)	Referent
High	2057 (25.0)	22 (19.5)	1.3 (0.7,2.4)	9 (15.3)	0.8 (0.3,1.8)
Minerals					
Iron (mg)					
Low	2057 (25.0)	33 (29.2)	0.9 (0.5,1.4)	18 (30.5)	0.8 (0.4,1.6)
Medium	4114 (50.0)	62 (54.9)	Referent	33 (55.9)	Referent
High	2057 (25.0)	18 (15.9)	0.8 (0.4,1.4)	8 (13.6)	0.6 (0.3,1.5)
Magnesium (mg)					
Low	2058 (25.0)	37 (32.7)	1.1 (0.7,1.8)	17 (28.8)	0.7 (0.3,1.3)
Medium	4113 (50.0)	55 (48.7)	Referent	33 (55.9)	Referent
High	2057 (25.0)	21 (18.6)	1.2 (0.6,2.4)	9 (15.3)	1.0 (0.4,2.5)
Manganese (mg)					
Low	2057 (25.0)	26 (23.9)	0.7 (0.4,1.2)	15 (25.4)	0.7 (0.4,1.3)
Medium	4114 (50.0)	66 (57.5)	Referent	31 (52.5)	Referent
High	2057 (25.0)	21 (18.6)	0.9 (0.5,1.6)	13 (22.0)	1.3 (0.6,2.6)
Phosphorus (mg)					
Low	2057 (25.0)	37 (32.7)	1.1 (0.7,1.9)	17 (28.8)	0.6 (0.3,1.2)
Medium	4114 (50.0)	54 (47.8)	Referent	31 (52.5)	Referent
High	2057 (25.0)	22 (19.5)	1.2 (0.6,2.3)	11 (18.6)	1.8 (0.7,4.4)
Selenium (μg)					
Low	2057 (25.0)	34 (30.1)	0.9 (0.6,1.5)	17 (28.8)	0.7 (0.3,1.3)
Medium	4114 (50.0)	61 (54.0)	Referent	32 (54.2)	Referent

Exposure	Controls (*N* = 8228)	All cases (*N* = 113)		Isolated cases (*N* = 59)	
	N	*N*	aOR (95% CI)[a]	*N*	aOR (95% CI)[b]
High	2057 (25.0)	18 (15.9)	0.9 (0.4,1.6)	10 (17.0)	1.1 (0.5,2.7)
Sodium (mg)					
Low	2057 (25.0)	40 (35.4)	1.4 (0.9,2.2)	20 (33.9)	0.9 (0.5,1.8)
Medium	4114 (50.0)	54 (47.8)	Referent	31 (52.5)	Referent
High	2057 (25.0)	19 (16.8)	0.9 (0.5,1.7)	8 (13.6)	0.7 (0.3,1.7)
One-carbon compounds					
Betaine (mg)					
Low	2057 (25.0)	29 (25.7)	0.9 (0.5,1.4)	12 (20.3)	0.6 (0.3,1.3)
Medium	4114 (50.0)	57 (50.4)	Referent	32 (54.2)	Referent
High	2057 (25.0)	27 (23.9)	1.3 (0.8,2.1)	15 (25.4)	1.6 (0.8,3.0)
Choline (mg)					
Low	2057 (25.0)	38 (33.6)	1.2 (0.7,1.9)	20 (33.9)	0.9 (0.5,1.8)
Medium	4114 (50.0)	54 (47.8)	Referent	29 (49.2)	Referent
High	2057 (25.0)	21 (18.6)	1.2 (0.6,2.2)	10 (17.0)	1.1 (0.5,2.7)
Folate DFE					
Low	2057 (25.0)	34 (30.1)	0.9 (0.6,1.5)	18 (30.5)	0.8 (0.5,1.6)
Medium	4114 (50.0)	56 (49.6)	Referent	33 (55.9)	Referent
High	2057 (25.0)	23 (20.4)	1.1 (0.6,1.8)	8 (13.6)	0.6 (0.3,1.4)
Methionine (g)					
Low	2057 (25.0)	43 (38.1)	**1.6 (1.0,2.6)**	20 (33.9)	0.9 (0.5,1.8)
Medium	4114 (50.0)	47 (41.6)	Referent	27 (45.8)	Referent
High	2057 (25.0)	23 (20.4)	1.4 (0.7,2.5)	12 (20.3)	1.6 (0.7,3.7)
Riboflavin (mg)					
Low	2057 (25.0)	30 (26.6)	0.8 (0.5,1.3)	14 (23.7)	0.6 (0.3,1.1)
Medium	4114 (50.0)	59 (52.2)	Referent	33 (55.9)	Referent
High	2057 (25.0)	24 (21.2)	1.2 (0.7,2.0)	12 (20.3)	1.3 (0.6,2.8)
Vitamin B-12 (mg)					
Low	2057 (25.0)	36 (31.9)	1.3 (0.8,2.1)	19 (32.2)	1.0 (0.5,1.8)
Medium	4114 (50.0)	47 (41.6)	Referent	28 (47.5)	Referent
High	2057 (25.0)	30 (26.6)	**1.9 (1.1,31)**	12 (20.3)	1.2 (0.6,2.6)
Vitamin B-6 (mg)					
Low	2057 (25.0)	35 (31.0)	1.1 (0.7,1.7)	19 (32.2)	0.9 (0.5,1.7)
Medium	4115 (50.0)	53 (46.9)	Referent	29 (49.2)	Referent
High	2057 (25.0)	25 (22.1)	1.6 (0.9,2.7)	11 (18.6)	1.2 (0.5,2.6)
Zinc (mg)					
Low	2057 (25.0)	39 (34.5)	1.4 (0.8,2.2)	18 (30.5)	0.8 (0.4,1.6)
Medium	4114 (50.0)	47 (41.6)	Referent	27 (45.8)	Referent
High	2057 (25.0)	27 (23.9)	**1.7 (1.0,3.1)**	14 (23.7)	1.9 (0.9,3.9)
Other vitamins					
Niadn (mg)					
Low	2057 (25.0)	40 (35.4)	1.4 (0.9,2.3)	22 (37.3)	1.3 (0.7,2.5)

Exposure	Controls (*N* = 8228)	All cases (*N* = 113)		Isolated cases (*N* = 59)	
	N	*N*	aOR (95% CI)[a]	*N*	aOR (95% CI)[b]
Medium	4114 (50.0)	46 (40.7)	Referent	24 (40.7)	Referent
High	2057 (25.0)	27 (23.9)	**1.8 (1.0,3.1)**	13 (22.0)	1.7 (0.8,3.7)
Pantothenic acid (mg)					
Low	2057 (25.0)	32 (28.3)	0.9 (0.5,1.4)	13 (22.0)	**0.4 (0.2,0.9)**
Medium	4114 (50.0)	60 (53.1)	Referent	36 (61.0)	Referent
High	2057 (25.0)	21 (18.6)	0.9 (0.5,1.7)	10 (17.0)	0.9 (0.4,2.0)
Vitamin A (μg *1U*)					
Low	2057 (25.0)	35 (31.0)	1.2 (0.7,1.8)	16 (27.1)	0.8 (0.4,1.4)
Medium	4114 (50.0)	55 (48.7)	Referent	34 (57.6)	Referent
High	2057 (25.0)	23 (20.4)	1.1 (0.7,1.9)	9 (15.3)	0.6 (0.3,1.4)
Vitamin C (mg)					
Low	2057 (25.0)	31 (27.4)	0.8 (0.5,1.3)	17 (28.8)	0.8 (0.4,1.5)
Medium	4114 (50.0)	63 (55.8)	Referent	33 (55.9)	Referent
High	2057 (25.0)	19 (16.8)	0.9 (0.5,1.7)	9 (15.3)	0.7 (0.3,1.6)
Vitamin K (mg)					
Low	2057 (25.0)	36 (31.9)	1.2 (0.8,1.9)	17 (28.8)	1.0 (0.5,1.9)
Medium	4114 (50.0)	51 (45.1)	Referent	27 (45.8)	Referent
High	2057 (25.0)	26 (23.0)	1.2 (0.7,2.0)	15 (25.4)	1.3 (0.7,2.5)
Vitamin D (mg)					
Low	2057 (25.0)	40 (35.4)	**1.6 (1.0,2.4)**	17 (28.8)	1.0 (0.6,1.9)
Medium	4114 (50.0)	46 (40.7)	Referent	27 (45.8)	Referent
High	2057 (25.0)	27 (23.9)	1.3 (0.8,2.2)	15 (25.4)	1.6 (0.8,3.1)

aOR, Adjusted Odds Ratio; CI, Confidence Interval; DFE, Dietary Folate Equivalent; IU, International Units; Low, <25 percentile; Medium, 25–75 percentile; High, >75 percentile.

Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data. Bold aOR and 95% CI indicate p-value < 0.05.

[a] Adjusted for infant sex, gestational age, birth weight, and plurality; and maternal race/ethnicity, type 1 or 2 diabetes before index pregnancy, history of hypertension, season of conception, and total energy intake in kilo calories.

[b] Adjusted for infant sex and gestational age; and maternal type 1 or 2 diabetes before index pregnancy, history of hypertension, season of conception, and total energy intake in kilo calories.

Table 3

Multivariable analyses for maternal caffeine consumption and choanal atresia, The National Birth Defects Prevention Study 1997–2007.

Exposure	Controls (*N* = 8350)	All cases (*N* = 117)		Isolated cases (*N* = 61)	
	N (%)	*N* (%)	aOR (95% CI)[b]	*N* (%)	aOR (95% CI)[c]
Coffee (cups/day) [a]					
<1	5768 (69.1)	75 (64.1)	Referent	33 (54.1)	Referent
1–2	1999 (23.9)	32 (27.4)	1.2 (0.8, 1.8)	20 (32.8)	1.7 (1.0,3.1)
≥3	578 (6.9)	10 (8.6)	1.1 (0.6,2.2)	8 (13.1)	**2.5 (1.1,5.6)**
Tea (cups/day)					
<1	6787 (81.3)	99 (84.6)	Referent	50 (82.0)	Referent
1–2	1184 (14.2)	12 (10.3)	0.6 (0.3,1.2)	8 (13.1)	0.9 (0.4,1.9)
≥3	369 (4.4)	6 (5.1)	1.0 (0.4,2.3)	3 (4.9)	1.2 (0.4,3.8)
Soda[d] (*cans, glasses or bottles/day*)					
<1	3476 (41.6)	60 (51.3)	Referent	29 (47.5)	Referent
1–2	2117 (25.4)	22 (18.8)	0.5 (0.3,0.9)	13 (21.3)	0.7 (0.4,1.4)
≥3	1219 (14.6)	20 (17.1)	0.7 (0.4,1.3)	10 (16.4)	0.9 (0.4,1.9)
Total caffeine (mg/day)					
<100 (none/very low)	3505 (42.0)	47 (40.2)	Referent	21 (34.4)	Referent
100–<200 (low)	1625 (19.5)	25 (21.4)	1.1 (0.7,1.9)	14 (23.0)	1.5 (0.7,2.9)
200–<300 (moderate)	897 (10.7)	19 (16.2)	1.4 (0.8,2.4)	10 (16.4)	1.9 (0.9,4.0)
≥300 (high/very high)	778 (9.3)	11 (9.4)	0.8 (0.4,1.5)	7 (11.5)	4.4 (0.5,3.6)

aOR, Adjusted Odds Ratio; CI, Confidence Interval; mg, milligrams; N, Frequency.

Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data. Bold aOR and 95% CI indicate *p*-value < 0.05.

[a] Cochran–Armitage Test for Trend significant for Isolated Cases ($p < 0.05$).

[b] Adjusted for infant sex, gestational age, birth weight, and plurality; and maternal race and ethnicity, type 1 or 2 diabetes before index pregnancy, history of hypertension, and season of conception.

[c] Adjusted for infant sex and gestational age; and maternal type 1 or 2 diabetes before index pregnancy, history of hypertension, and season of conception.

[d] Frequency of caffeinated soda was calculated by categorizing milligrams of caffeine per day using the following cutoff values: <34 mg = <1 serving; 34–<102 mg = 1–2 servings; 102 + mg = ≥3 servings.

Table 4

Multivariable analyses for maternal periconceptional cigarette smoking or alcohol and choanal atresia, The National Birth Defects Prevention Study 1997–2007.

Exposure	Controls (*N* = 8350)	All cases (*N* = 117)		Isolated cases (*N* = 61)	
	N (%)	*N* (%)	aOR (95% CI)[a]	*N* (%)	aOR (95% CI)[b,c]
Cigarette smoking					
None	5664 (67.8)	77 (65.8)	Referent	36 (59.0)	Referent
Any exposure	2664 (32.0)	38 (32.5)	0.9 (0.6,1.4)	24 (39.3)	1.4 (0.8,2.3)
Type of smoking					
Active only	626 (7.5)	11 (9.4)	1.1 (0.6,2.1)	9 (14.8)	**2.3 (1.1,4.7)**
Passive only	1127 (13.5)	19 (16.2)	1.3 (0.8,2.2)	9 (14.8)	1.3 (0.6,2.6)
Active and Passive	910 (10.9)	9 (7.7)	0.5 (0.2,1.1)	6 (9.8)	0.9 (0.3,2.2)
Cigarettes/day					
1–14	1072 (12.8)	14 (12.0)	0.7 (0.4,1.3)	12 (19.7)	1.6 (0.8,3.0)
≥15	449 (5.4)	5 (4.3)	0.5 (0.2,1.4)	3 (4.9)	1.0 (0.3,3.1)
Alcohol consumption					
None	5239 (62.7)	71 (60.7)	Referent	36 (59.0)	Referent
Any exposure	3039 (36.4)	44 (37.6)	1.0 (0.7,1.5)	24 (39.3)	1.2 (0.7,2.0)
Average drinks/month					
1–15	2348 (28.1)	36 (30.8)	1.1 (0.7,1.6)	19 (31.2)	1.2 (0.7,2.2)
≥16	657 (7.9)	7 (6.0)	0.8 (0.3,1.7)	5 (8.2)	1.1 (0.4,2.9)
Binge episodes (≥*4 drinks*)					
Drinking, no binge episodes	2019 (24.2)	34 (29.1)	0.7 (0.3,1.3)	18 (29.5)	1.4 (0.8,2.4)
Drinking, ≥1 binge episodes	993 (11.9)	9 (7.7)	1.2 (0.8,1.8)	6 (9.8)	0.9 (0.4,2.1)

aOR, Adjusted Odds Ratio; CI, Confidence Interval; N, Frequency; Periconceptional period corresponded to the month prior to conception (B1) through the first three months of pregnancy (M1, M2, and M3).

Frequency of cases and controls may vary because of missing data. Percentages may not equal 100 because of missing data. Bold aOR and 95% CI indicate *p*-value < 0.05.

[a] Cigarette smoking and alcohol consumption variables - adjusted for infant sex, gestational age, birth weight, and plurality; and maternal race and ethnicity, type 1 or 2 diabetes before index pregnancy, history of hypertension, and season of conception.

[b] Cigarette smoking variables only - adjusted for infant sex and gestational age; and maternal type 1 or 2 diabetes before index pregnancy, history of hypertension, and season of conception.

[c] Alcohol consumption variables only - adjusted for infant sex, gestational age, and birth weight; and any maternal periconceptional active smoking, type 1 or 2 diabetes before index pregnancy, history of hypertension, and season of conception.